Alkylating Agents

ONE of the most frequent tasks the organic chemist is called upon to perform is that of alkylation. Almost constantly he wants to do such things as make an ether from a phenol or alcohol, a secondary or tertiary amine from the primary amine, or an ester from a carboxylic acid. Until comparatively recently the chief reagents for introducing an alkyl group into a molecule were the alkyl halides. These, however, were not satisfactory because the chlorides were too unreactive, and the bromides and iodides were very expensive, especially in view of the fact that such a small weight of alkyl group, as compared with the weight of the halogen, is present in the molecule. So a search for better alkylating reagents was made and several were developed.

Chief among the improved reagents are the alkyl esters of sulfur acids, i.e., the alkyl sulfates, sulfites, and p-toluenesulfonates; the alkyl sulfates being the best known and most important. Chemists have long been familiar with methyl sulfate but prior to 1900, when its actual development began, it was somewhat of a rarity rather than a valuable laboratory tool. Today it has extensive commercial use and tons of it are made.

Methyl sulfate reacts with both aliphatic and aromatic mono- and polyatomic hydroxy compounds to form the methyl ethers; with the corresponding thio compounds to form the thio ethers; with primary amines to give secondary or tertiary amines; with sodium or potassium salts of organic acids to form methyl esters. It can also be used with inorganic sodium salts to prepare organic compounds. Thus, methyl sulfate, with sodium hydrogen sulfide, yields methyl mercaptan; with sodium sulfide, methyl sulfide; with sodium nitrite, methyl nitrite.

Methyl sulfate is an extremely active substance and one of its two methyl groups will ordinarily react readily at room temperatures. In order to make use of the second methyl group some heating is required. Where cost is not a prime consideration, the methylation may be run at a lower temperature, making use of only one of the methyl groups. Such a procedure is very advantageous in the methylation of carbohydrates and glucosides. Formerly, methyl iodide was used in preparing the methyl ethers, and high temperatures, sometimes even sealed tubes were required. Now, methyl sulfate produces the same results at ordinary temperatures, thus avoiding the possibility of change in configuration under the influence of heat.

Ethyl sulfate was first made in 1848 by Wetherill, from sulfur trioxide and absolute ether, but only in the last ten years has it been available in large quantities. It is quite analogous to methyl

sulfate, in its behavior and will react with the same compounds. However, it is not quite so active as methyl sulfate and requires slightly higher temperatures; the first group reacting at 50 to 55° C. in most instances, and the second, at about 145° C. One useful application of ethyl sulfate is that of lengthening a carbon chain by addition of two carbon atoms.

Ethyl sulfate reacts with the Grignard reagent in the following fashion: $RMgX + (Et)_2SO_4 \longrightarrow REt + Et(MgX)SO_4$. This reaction takes place whether R is alkyl or aryl. Ethyl sulfate has also been used to alkylate imides, using the potassium salt of the imide. In many of the reactions of ethyl sulfate, an inert solvent, such as benzene or naphtha, may be used if it is desirable.

In general, the alkyl sulfates possess the following advantages over the alkyl bromides and iodides:

1. They are much less expensive.
2. The action of the first alkyl group is very rapid.
3. The alkylation in many cases can be carried out at lower temperatures.
4. They give better yields.
5. Their high boiling points permit alkylation in open flasks instead of requiring sealed tubes.
6. They do not require the lengthy working-up of bromide or iodide residues which must be recovered when large quantities are involved.

The use of alkyl sulfates is limited to the methyl and ethyl compounds because the higher analogues either cannot be prepared or can be obtained only in poor yields and with great difficulty. In recent years the higher alcohols have become available in large quantities at a low cost and this naturally has stimulated a desire to work with the larger alkyl groups where formerly only methyl and ethyl were used. In such alkylations the alkyl sulfites can be employed.
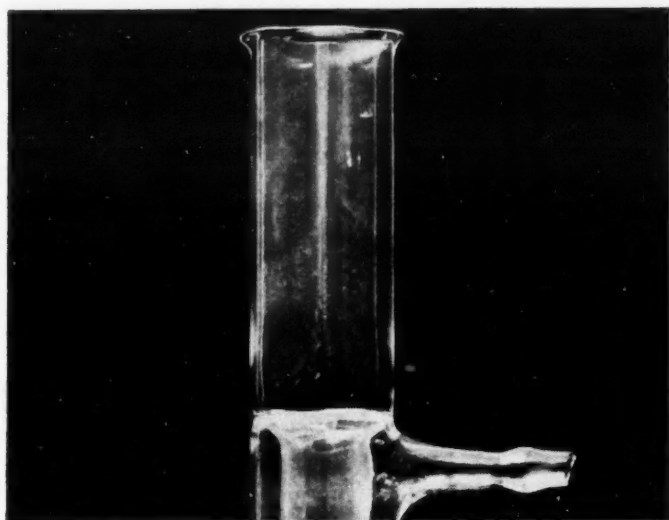
The reactions of the alkyl sulfites are described in a recent article by Voss and Blanke, Ann. *485*, 250 (1931). They show that aromatic ethers, secondary and tertiary amines, and carboxylic esters with higher alkyl groups, can be successfully prepared from the alkyl sulfites. One limitation to be noted, however, is that alkyl sulfites cannot be used in aqueous alkaline solution because they are hydrolyzed too readily. Sodium derivatives of the compound to be alkylated are employed with the sulfites to avoid the aqueous alkali used with sulfates. The alkyl sulfites can be used to form glucosides of sugars and acetals of aldehydes and ketones. The latter fact is especially interesting, since the acetals of aromatic aldehydes and ketones, which formerly were extremely difficult to obtain, can now be readily prepared from the sulfites.

The p-toluenesulfonic esters have been used for some time, with increasingly satisfactory results, for introducing methyl and ethyl groups. The esters of p-toluenesulfonic acid should not be overlooked in connection with the introduction of higher alkyl groups. In a recent article, Ber. *63B*, 678-691 (1930), Slotta and Franke demonstrated that the higher alkyl, as well as the methyl or ethyl esters may be used for alkylations, giving splendid results. Aliphatic and aromatic ethers and thioethers, secondary and tertiary aromatic amines, and heterocyclic alkylated amines can be prepared from these esters. Some alkylations to a carbon atom, as in the preparation of propylmalonic ester, also give good yields. Like the alkyl sulfites, the higher alkyl p-toluenesulfonic esters are just beginning to be used as alkylating agents, and their scope of application probably will be widened.

Because of their many advantages, it appears that in most cases the esters of sulfur acids will gradually displace the alkyl halides as alkylating agents.
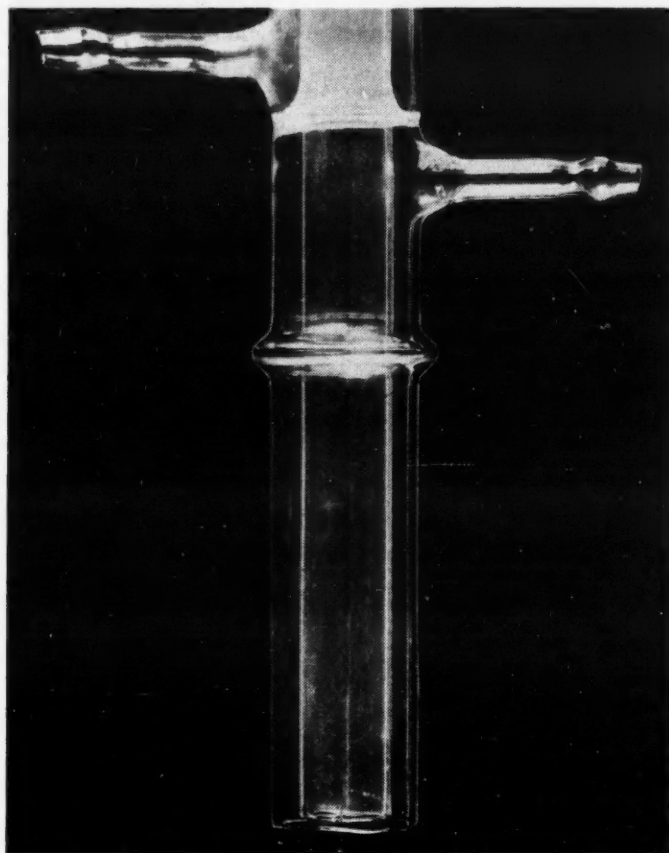
A Rugged Glass Condenser

THE glass condenser pictured on this page has several advantages not found in the usual types. It consists of two tubes sealed together in such a way that the joints are strongly united, with very little internal strain. The glass blowing is not difficult and the resulting product is quite rugged, being able to withstand most of the mechanical shocks to which condensers are ordinarily subjected.

Lower end of condenser

Top of condenser

It is superior to the two-piece type condensers because the jacket is joined to the tube without the use of rubber connectors which gradually deteriorate when subjected to high temperatures and allow the condenser water to leak through. This one-piece type is especially advantageous when several condensers are connected in series to one water tap, since there are no weakened rubber connections to be forced out by the increased pressure.
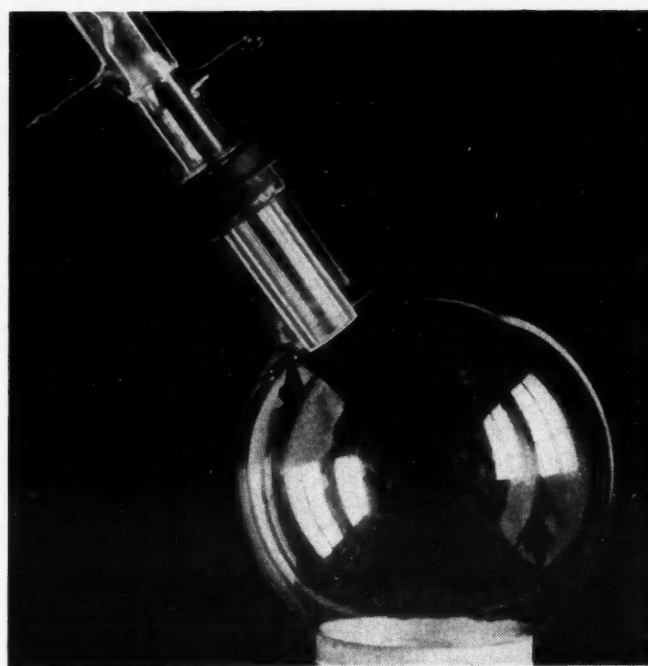
The arrangement at the lower end is very convenient for vacuum distillations. As only one hole is needed in the stopper of the receiving flask, the possibility of pressure leakage is minimized. Two other modifications which have been mentioned in previous articles are also incorporated. They are: the indentations in the inner tube to increase the condensing surface; the shoulder at the lower end of the condenser, which makes the connection to the stopper more secure.

Constructional details including the two inner seals can be seen in the accompanying illustrations.

Receiving flask equipped for vacuum distillation

Eastman Organic Chemicals as Analytical Reagents

XXII   Reagents for Boron.

CURCUMIN

Cassal & Gerrans, CHEM. NEWS, *87*, 27 (1903)

The substance under examination is treated with a small amount of hydrochloric and oxalic acids and then with a 0.1% solution of curcumin in alcohol. After evaporating to dryness on the water bath, the mixture is digested with alcohol. In the presence of even a small quantity of boric acid, an intense magenta coloration is produced. With suitable precautions the reaction can be used to determine borates quantitatively.

MANNITOL

Scott, STANDARD METHODS OF ANALYSIS p. 90 (1927)

Boric acid in the presence of stronger acids is determined by first exactly neutralizing the solution, using para nitrophenol as an indicator. Boric acid is much too weak to affect the indicator. A few drops of phenolphthalein solution and one gram of mannitol are then added and the solution titrated with tenth-normal alkali to the change in color at the phenolphthalein end point. The combination of the mannitol and boric acid results in a complex which is a much stronger acid than boric, and which can be readily titrated.

METHYL ALCOHOL

Gabriel & Tanner, J.A.C.S. *50*, 1385 (1928)

A solution suspected of containing a borate is made slightly alkaline with sodium hydroxide and evaporated nearly to dryness. After treating the residue with 1 cc. of concentrated sulfuric acid and cooling, 2 cc. of methyl alcohol are added and the solution transferred to a test tube. Air is then blown through the warmed solution and the vapors expelled through a capillary tube. If the exit stream contains any methyl borate, it will impart a characteristic green color to a Bunsen flame. As little as 0.2 mg. boric acid can be detected.

Thirty-three New Eastman Organic Chemicals

Since the publication of the Supplementary List of Eastman Organic Chemicals on October 1, the following new items have been added to our stock. Purity specifications and prices for any of these compounds will be supplied on request.

Benzalaniline
o-Bromophenetole
p-Cyclohexylanisole
Dibenzyl Maleate
2.6-Dibromophenol
p.p'-Dinitrodiphenyl Ether
s-Di-p-tolyl-thiourea
o-Ethylaniline
p-Ethylaniline
Ethylene Glycol Monobenzyl Ether
p-Fluorobromobenzene
n-Heptylamine
Hydantoin
Hydroquinone Diethyl Ether
a-Hydroxy-iso-Butyric Acid
p-Methoxybenzophenone
p-Methoxydiphenyl
o-Methylcyclohexanone
m-Methylcyclohexanone
p-Methylcyclohexanone
Methyl iso-Propyl Ketone
Pentamethylbenzene
Tetrahydrofurfuryl Benzoate
Tetrahydrofurfuryl Butyrate
Tetrahydrofurfuryl n-Caproate
Tetrahydrofurfuryl Lactate
Tetrahydrofurfuryl Laurate
Tetrahydrofurfuryl Maleate
Tetrahydrofurfuryl Palmitate
N-o-Tolylpyrrole
N-m-Tolylpyrrole
N-p-Tolylpyrrole
Trimethylene Chlorobromide